CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212295Orig1s000

Trade Name:	BYFAVO (remimazolam) for injection, for intravenous use, 20 mg per vial.
Generic or Proper Name:	remimazolam
Sponsor:	Cosmo Technologies, Ltd.
Approval Date:	July 2, 2020
Indication:	Indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less

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212295Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 212295

NDA APPROVAL

Cosmo Technologies, Ltd.
c/o Conventus Biomedical Solutions, Inc.
5414 Oberlin Drive, Suite 130
San Diego, CA 92121

Attention: Steve A. Kradjian, RAC
U.S. Agent, Conventus Biomedical Solutions, Inc.

Dear Mr. Kradjian:

Please refer to your new drug application (NDA) dated and received April 5, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYFAVO (remimazolam) for injection, for intravenous use, 20 mg per vial.

We acknowledge receipt of your major amendments dated January 31, and February 24, 2020, which extended the goal date by three months.

This new drug application provides for the use of BYFAVO for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of remimazolam under the Controlled Substances Act (CSA). The scheduling of this product in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the date of approval for BYFAVO shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of remimazolam.

We note that, when the drug is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information, and carton and container labeling by submitting a supplement to your NDA. This would include the statements in the labeling detailing the scheduling of remimazolam, as the scheduled substance in

BYFAVO, as required under 21 CFR 201.57(a)(2) and (c)(10)(i). Therefore, BYFAVO may be marketed only after DEA has published the notice in the Federal Register announcing the interim final scheduling of remimazolam and you submit a supplement to your NDA to revise all applicable drug labeling to reflect the drug scheduling described in the notice. For changes to the Prescribing Information, and carton and container labeling to describe the scheduling of BYFAVO, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights of Prescribing Information for BYFAVO described in 21 CFR 314.70(b)(2)(v)(C).

We note that BYFAVO will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of remimazolam.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to carton and container labeling submitted on June 30, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212295**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of the following pediatric studies according to the timetables listed below because this product is ready for approval for use in adults and the pediatric studies have not been completed. These required studies are listed below.

3889-1 Conduct a multicenter, sequential age-group study to evaluate the pharmacokinetics, safety, and efficacy of BYFAVO administered for procedural sedation in pediatric patients three to less than 17 years of age.

Final Protocol Submission:	08/2020
Study Completion:	07/2024
Final Report Submission:	01/2025

3889-2 Conduct a multicenter study to evaluate the pharmacokinetics, safety, and efficacy of BYFAVO administered for procedural sedation in pediatric patients from birth to less than three years of age.

Draft Protocol Submission:	01/2025
Final Protocol Submission:	07/2025
Study Completion:	07/2028
Final Report Submission:	01/2029

3889-3 Conduct a juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under 3 years of age.

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Study Completion:	06/2022
Final Report Submission:	12/2022

3889-4 Conduct a juvenile animal toxicology study in a nonrodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under three years of age.

Draft Protocol Submission:	03/2021
Final Protocol Submission:	09/2021
Study Completion:	06/2024
Final Report Submission:	12/2024

3889-5 Conduct a juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support a clinical indication for use in pediatric patients greater than or equal to three years of age and below 18 years of age.

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Study Completion:	06/2022
Final Report Submission:	12/2022

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit the protocol(s) to your IND 102486, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse reproductive and developmental effects of remimazolam.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3889-6 Conduct a male fertility study testing the drug product formulation that evaluates reproductive behavior and fertility and obtains pharmacokinetic analysis in a species that supports the maximum clinical exposures (C_{max} and AUC) achieved with the proposed clinical indication.

The timetable you submitted on June 17, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Study Completion:	12/2021
Final Report Submission:	06/2022

3889-7 Conduct an embryo-fetal development study testing the drug product formulation in a species other than the rabbit that supports the maximum clinical exposures (C_{max} and AUC) achieved with the proposed clinical indication.

The timetable you submitted on June 17, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Study Completion:	06/2022
Final Report Submission:	12/2022

3889-8 Conduct a pre-and post-natal development study testing the drug product formulation that evaluates all standard endpoints including learning, memory, and reproductive function of the F1 offspring and obtains adequate toxicokinetic data in a species that supports the maximum clinical exposures (C_{max} and AUC) achieved with the proposed clinical indication.

The timetable you submitted on June 17, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Study Completion:	12/2022
Final Report Submission:	06/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

EXPIRATION DATING

BYFAVO (remimazolam) for injection, for intravenous use, 20 mg per vial, is granted an expiry dating of 36 months when stored at 20°C –25°C (68°F -77°F) with excursions permitted between 15° - 30°C (59° and 86° F), and protected from light.

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[8]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Taiye Adedeji, PharmD, Regulatory Project Manager, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Mary Thanh Hai, MD
Acting Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY T THANH HAI
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